

REMARKS

I. Status of the Claims

Claims 1 and 4-7 are currently pending. With this Reply, claim 1 is amended.

No new matter is added by this Reply. By this Reply, Applicants withdraw the Notice of Appeal with the Board of Patent Appeals and Interferences and respond to the rejection of record in the final Office Action dated February 26, 2004, as well as the remarks made in the Advisory Action dated June 1, 2004, and January 18, 2005, and the Office's remarks made in the Examiner's Answer dated May 6, 2005.

II. Rejection under 35 U.S.C. § 103

The Office has rejected claims 1 and 4-7 under 35 U.S.C. § 103 as unpatentable over RO 92436 to Buzas et al. ("Buzas"). Office Action dated August 14, 2003 at page 6; see also, Office Action dated February 26, 2004. Applicants continue to respectfully disagree and traverse this rejection.

To establish a *prima facie* case of obviousness, the Office must meet three basic criteria. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. M.P.E.P. § 2143 (8th ed. Rev. 2, 2004).

"The examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness." M.P.E.P. § 2142. In doing so, "all the words in a claim

must be considered in judging the patentability of the claim against the prior art.” *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). Further, it is not sufficient to merely “find every element of a claimed invention in the prior art [and for] an examiner to use the claimed invention itself as a blue print for piecing together elements . . . Such an approach would be an illogical and inappropriate process by which to determine patentability.” *In re Rouffet*, 149 F.3d 1350, 1357, 47 U.S.P.Q.2d 1453, 1457 (Fed. Cir. 1998) (citations and quotations omitted). Instead, the art must suggest the desirability of the modifications. *See In re Gordon*, 733 F.2d 900, 902, 221 U.S.P.Q.2d 1125, 1127 (Fed. Cir. 1984) (“The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification.”).

Under the Office’s rationale, Buzas teaches a composition comprising a carbonic anhydrase inhibitor and a beta-blocker such as pindolol to treat gastritis, gastro-duodenitis, and gastro-duodenal ulcers. Office Action dated August 14, 2003, at page 6. The Office concedes that Buzas does not teach S(-)pindolol, but asserts that “since it is known that pindolol is an antagonist of 5HT1a, it is reasonable to expect that S(-)pindolol would also have those properties.” *Id.* According to the Examiner, the “comprising” language used in Applicants’ previously pending claims does not exclude the combination of carbonic anhydrase inhibitors with pindolol and Buzas therefore renders those claims obvious. Office Action dated February 26, 2004, at page 3.

With the amended claims presented herein, the claimed invention excludes the synergistic combination of pindolol with carbonic anhydrase inhibitors in view of the

change of the transitional phrase “comprising” to “consisting essentially of.” The Office, however, contends that the addition of the carbonic anhydrase inhibitor of Buzas would not *materially* change the characteristics of Applicants’ pindolol composition and that the teachings in Buzas continue to render obvious the presently claimed invention.

Advisory Action dated June 1, 2004. In addition, the Office asserts that because synergy means “the interaction of two or more treatments such that their combined effect is greater than the sum of the individual effects observed when each treatment is administered alone,” Buzas teaches that pindolol used alone can treat gastrointestinal disease, but has a greater effect when administered together with a carbonic anhydrase inhibitor. Advisory Action dated January 18, 2005.

Applicants submit that, among other things, the transitional phrase “consisting essentially of” excludes compounds such as the carbonic anhydrase inhibitors taught in Buzas that produce a synergistic effect when combined with S(-) pindolol and, furthermore, that there is no suggestion or motivation to modify the teachings of Buzas to omit the carbonic anhydrase inhibitor.

The transitional phrase “consisting essentially of” renders a claim open for the inclusion of only unspecified ingredients that do not “*materially affect* the basic and novel characteristics of the claimed composition.” *Dow Chemical Co. v. American Cyanamid Co.*, 615 F. Supp. 471, 484, 229 U.S.P.Q. 171, 180 (E.D. La. 1985), *aff’d*, 816 F.2d 617, 2 U.S.P.Q.2d 1350 (Fed. Cir. 1987) (emphasis added). The “consisting essentially of” claim occupies middle ground between the closed transitional phrase “consisting of” and the open transitional phrase “comprising.” See M.P.E.P. § 2111.03.

The Federal Circuit discussed in *PPG Industries v. Guardian Industries Corp.*, 156 F.3d 1351, 48 U.S.P.Q.2d 1351 (Fed. Cir. 1998), *inter alia*, what constitutes a “material effect.” The claim of interest read:

A green tinted, ultraviolet absorbing glass having a base glass composition consisting essentially of . . . and a colorant portion consisting essentially of [ferrous or ferric iron and cerium oxide].

Guardian argued that its glass did not infringe because it contained iron sulfide, which was not listed as a colorant in PPG’s patent. *Id.* at 1353, 48 U.S.P.Q.2d at 1353. PPG argued that iron sulfide was an inherent by-product of the float glass manufacturing process used by both Guardian and PPG. *Id.* at 1354, 48 U.S.P.Q.2d at 1353. PPG also pointed to a passage in the specification that stated “[m]elting and fining aids such as SO₃ are useful during production of the glass, but their residual amounts in the glass may vary and have no significant effect on the properties of the glass product.” *Id.* at 1355-56, 48 U.S.P.Q.2d at 1355.

The Federal Circuit held that there was substantial evidence from which the jury could conclude that the iron sulfide in the glass had a material effect on the basic and novel properties of the glass. *Id.* at 1357, 48 U.S.P.Q.2d at 1356. Under this holding, the court highlighted evidence indicating that those skilled in the art would regard even small changes in the color or transmittance of tinted glass to be material, measurable, reproducible changes that cannot be attributed to experimental error. *Id.* at 1357, 48 U.S.P.Q.2d at 1357. Thus, despite the specification generally suggesting that sulfur compounds have insignificant effects on the properties of the glass, the court found that

sulfur in the glass in the form of iron sulfide is a strong colorant and that even small changes in color are material parameters important to the skilled artisan.

In *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 68 U.S.P.Q.2d 1280 (Fed. Cir. 2003), the patent of interest covered hot dip aluminum-coated stainless steel and the issue was whether an amount of silicon in excess of 0.5% in the aluminum coating materially affected the basic and novel properties of the invention. 344 F.3d at 1236, 1239, 68 U.S.P.Q.2d at 1282, 1283. In this case, the specification of the patent of interest was far from silent with regard to silicon's affect on the properties of the aluminum coating bath and the resultant coated steel. *Id.* at 1240, 68 U.S.P.Q.2d at 1283-84. As the Federal Circuit explained, the patent expressly provided that the silicon content should not exceed 0.5% or the aluminum coating would not adhere well to steel. *Id.*, 68 U.S.P.Q.2d at 1284. Despite AK Steel's attempt to argue that the statements in the specification were merely explaining a scientific theory and as such, should not be used to limit the claimed invention, the court indicated that conclusions speaking to the conditions under which the invention will or will not operate are not theory and thus, impact the meaning of the claim phrase "consisting essentially of aluminum." *Id.*, 68 U.S.P.Q.2d at 1284. Accordingly, the specification directly spoke to the effects of silicon on the properties of aluminum coating bath, and the court held as a matter of claim construction that the claims do not encompass steel coated with aluminum containing more than about 0.5% silicon.

Applying the legal principles established by these cases to the current situation, one should at least look to the present specification to determine what could be

considered to materially affect the basic and novel properties of the present invention. Although the specification lacks a definitive statement with regard to carbonic anhydrase inhibitors as in *AK Steel*, Applicants submit that on page 4, lines 14-17 of the specification, an aspect of the present invention, is “the administration of effective amounts of a substance” leading to beneficial effects in subjects suffering from non-ulcerative dyspepsia. As such, the question is whether the addition of a carbonic anhydrase inhibitor taught in Buzas to a composition of pindolol would have a material effect on the basic and novel characteristics of the claimed method. To answer this question, one need only look to the disclosure in Buzas.

Buzas teaches that carbonic anhydrase inhibitors, when used in combination with certain other specified compounds (including some beta-blockers like pindolol), provide a *synergistic* effect. Synergistic effects “demonstrate ‘an effect greater than the sum of the several effects taken separately.’” *Merck & Co. v. Biocraft Labs, Inc.*, 874 F.2d 804, 808, 10 U.S.P.Q.2d 1843 (Fed. Cir. 1989). In fact, “synergism may point toward nonobviousness” *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1540, 218 U.S.P.Q. 871, 880 (Fed. Cir. 1983) (explaining that synergism is not a requirement under an obviousness inquiry, but indicates nonobviousness). Given that synergistic effects, when present, point to nonobviousness, these effects are material.

Buzas’ synergistic compositions contain a carbonic anhydrase inhibitor and a beta-adrenergic blocker selected from among propranolol, atenolol, pindolol, timolol, oxprenolol, acebutolol, or metoprolol in a weight ratio in the range of 1.37 to 231. Buzas et al. Translation at page 2. Buzas states that “[t]he object of the present invention is to

obtain a *synergistic* pharmaceutical composition . . . [through the] selection of ingredients and the mixture ratio thereof.” *Id.* (emphasis added). Each of Buzas’ claims is also explicitly limited to “synergistic” combinations. “[A] reference must be considered for not only what it expressly teaches, but also for what it fairly suggests.” *In re Burckel*, 592 F.2d 1175, 1179, 201 U.S.P.Q. 67, 70 (C.C.P.A. 1979). Thus, achieving synergy appears to be Buzas’ whole basis for describing the use of such combination therapies. Nevertheless, the Office contends that Buzas “fairly suggests” that beta-blockers used alone produce therapeutic effects on gastrointestinal disorders. See Examiner’s Answer dated May 6, 2005 at page 6; Advisory Action dated January 18, 2005.

To the contrary, Buzas presents evidence confirming that beta-blockers used *alone* are not effective agents for treating gastrointestinal disorders. Buzas et al. Translation at page 8, Table 3. For example, Buzas measured the production of hydrochloric acid and the activity of carbonic anhydrase in human gastric mucosa and in red blood cells in patients with duodenal ulcers. *Id.* The results below, which are from Buzas, show that pindolol used alone did not differ from a control with respect to hydrochloric acid flow, especially considering the variability given. In addition, Buzas observed no difference between the effect of pindolol and a control on carbonic anhydrase activity in gastric mucosa cells and in red blood cells.

Beta-blocker	Hydrochloric Acid Flow (mEq/h)	Carbonic Anhydrase Activity in Gastric mucosa Cells	Carbonic Anhydrase Activity in Red Blood Cells
Control	9.87 ± 2.71	1.87 ± 0.13	2876 ± 139
Pindolol	7.98 ± 1.17	1.70 ± 0.31	2590 ± 113
Practolol	6.89 ± 1.65	1.58 ± 0.39	2476 ± 326

Id. at page 8, Table 3. Based on the data presented in Table 3, Buzas concludes that “*in vivo* administration of some *beta*-adrenergic blockers to patients with gastroduodenal disorders leads to slightly decreased gastric acid secretion parameters and carbonic anhydrase activity.” *Id.* at page 8. Nowhere does Buzas equate a “slight” decrease in gastric acid and carbonic anhydrase activity to therapeutic effects. Moreover, this “slight” decrease is found in only “some” of the beta blockers (arguably, e.g., practolol as illustrated in the table above).

Comparing beta-blockers alone and in conjunction with carbonic anhydrase inhibitors, one can see the “synergistic” action identified by Buzas. For example, Table 9 of Buzas reproduced in part below, illustrates this synergism.

Name	Hydrochloric Acid Flow (mEq/h)	Carbonic Anhydrase Activity
Control	9.87 ± 2.71	76 ± 22
Ethoxzolamide	3.87 ± 0.98	37 ± 17
Pindolol	7.98 ± 2.17	69 ± 22
Ethoxzolamide + Pindolol	0.71 ± 0.17	24 ± 3

Id. at page 12, Table 9.

The Patent Office's Final Written Description Guidelines provide that "if applicant contends additional steps or materials in the prior art are excluded by the recitation of 'consisting essentially of,' applicant has the burden of showing that the introduction of additional steps or components would materially change the characteristics of applicants invention." Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, para. 1, "Written Description" Requirement, 66 Fed. Reg. 1105, n.29 (January 5, 2001). This burden is met with the showings in Buzas, as detailed above.

Despite this evidence, the Office still contends that because the combination of pindolol with a carbonic anhydrase inhibitor is synergistic, Buzas suggests that "the beta-adrenergic blocker, such as pindolol, administered alone is *effective* in treating gastrointestinal disease, and when combined with the carbonic anhydrase inhibitor, the net effect is greater than when one agent is administered alone." Advisory Action dated

January 18, 2005 (emphasis added). There simply is no rational basis for the Office's conclusion, which appears, albeit unreasonably so, to be grounded in the Office's definition of synergy as "the interaction of two or more treatments such that their combined effect is greater than the sum of the individual effects observed when each treatment is administered alone." *Id.*

Buzas, however, clearly shows that there is a synergy, as defined, that occurs between a beta-adrenergic blocker and carbonic anhydrase inhibitors resulting in a greater effect than when one agent is used alone, but there is no evidence in Buzas to support the Examiner's conclusion that beta-adrenergic, i.e., pindolol, **MUST** be effective when used alone to treat gastrointestinal disease. In fact, Buzas presents data suggesting quite the opposite. Buzas demonstrates that pindolol alone is comparable to the control, especially when taking into consideration the standard deviation in the results. Buzas et al. at page 8, Table 3.

Furthermore, there is nothing in the Office's definition of "synergy" that requires that individual treatments must be effective when used alone, let alone *therapeutically* effective. The definition merely speaks to the combined effects being greater than the individual effects of each treatment. Thus, the asserted definition does not extrapolate on the *effectiveness* of the individual treatments, as does the Office. Accordingly, the leap of logic between the definition of synergy and its application to the current case presents the problem.

As in *PPG Industries*, Buzas' specification and data provide evidence from which a skilled artisan would conclude that adding a carbonic anhydrase inhibitor to a pindolol

composition would have a material effect. Buzas demonstrates the synergistic effects, i.e., results greater than the sum of the carbonic anhydrase inhibitor and pindolol taken separately. Moreover, Buzas concludes that the synergistic combination provides "therapeutic effects (reduced secretion parameters) and leads to healing . . ." whereas Buzas fails to draw such a conclusion with regard to pindolol used alone. Instead, Buzas provides only that there is a "slight" decrease in gastric acid secretion and carbonic anhydrase with pindolol alone. Buzas et al. Translation at pages 8 and 11.

Accordingly, the addition of a carbonic anhydrase inhibitor would materially alter a composition "consisting essentially of an effective amount of S(-)pindolol," as recited in the presently claimed invention, by producing a synergistic effect different from the effect of S(-)pindolol alone. Given this synergy, Applicants contend that the addition of carbonic anhydrase inhibitors would materially affect the basic and novel characteristics of the claimed invention. As the Office acknowledges, any elements having such an effect are excluded by a claim that recites, "consisting essentially of." See Advisory Action dated June 1, 2004; *see also*, *PPG Industries*, 156 F.3d at 1354, 48 U.S.P.Q.2d at 1353-54.

Thus, carbonic anhydrase inhibitors are properly excluded from the presently amended claims. Nothing in the cited prior art teaches or suggests the use of a composition that does not include carbonic anhydrase inhibitors. As such, Buzas' disclosures fail to teach or suggest all the claim limitations. See M.P.E.P. § 2143.

There simply is no clear and particular suggestion in the cited prior art to modify Buzas by omitting a carbonic anhydrase inhibitor from a composition intended for use in

treating gastrointestinal disorders. Buzas describes a *synergistic* composition containing a carbonic anhydrase inhibitor and a beta-adrenergic blocker in specific weight ratios. Buzas et al. Translation at page 2. According to Buzas, the object of the invention is to obtain a synergistic composition through the "selection of ingredients and the mixture ratio thereof." *Id.*

In fact, Buzas, as discussed above, suggests that beta-blockers, when used alone, are ineffective as a treatment for duodenal ulcers. See *id.* at page 8, Table 3. Buzas discloses that only after combining the beta-blockers with a carbonic anhydrase inhibitor (acetazolamide or ethoxzolamide) does one achieve a therapeutic effect. See *id.* at page 12, Table 9. Thus, Buzas reports that the combination might be therapeutic, but that beta-blockers alone are not. Buzas fails to provide any guidance to suggest or motivate one of ordinary skill in the art to use a beta-blocker as a mono-therapy for gastrointestinal conditions.

Proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. M.P.E.P. § 2146(X) (citing *In re Hedges*, 783 F.2d 1038, 228 U.S.P.Q. 685 (Fed. Cir. 1986)). As discussed, Buzas demonstrates that beta-blockers alone are an ineffective treatment for duodenal ulcers. Contrary to Buzas' teaching that only the combination of pindolol and a carbonic anhydrase inhibitor are effective, Applicants show that pindolol alone provides a substantial reduction in average symptom severity in patients suffering from non-ulcerative dyspepsia. Specification at page 7.

Moreover, there is no reasonable expectation of success to support modifying the teachings of Buzas in the manner proposed by the Office. Buzas, as discussed in detail above, suggests that beta-blockers alone are ineffective treatments for the one condition tested (duodenal ulcers). Given such guidance, one skilled in the art would have no reasonable expectation of successfully using pindolol or a stereoisomer of pindolol to treat the same disorder without first proving that Buzas was wrong. Accordingly, for at least these reasons, the Office failed to establish a prima facie case of obviousness and thus, Applicants respectfully request the withdraw of this rejection.

III. Conclusion

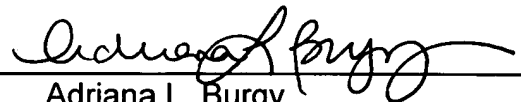
In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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